

Appendix A
Marked-Up Version of Amendments to Specification

Paragraph 5 on page 2 has been amended in the following manner:

[5] Matrix metalloproteinases, a family of zinc-dependent proteinases, make up a major class of enzymes involved in degrading connective tissue. Matrix metalloproteinases are divided into classes, with some members having several different names in common use. Examples are: MMP-1 (also known as collagenase 1, fibroblast collagenase, or EC 3.4.24.3); MMP-2 (also known as gelatinase A, 72kDa gelatinase, basement membrane collagenase, or EC 3.4.24.24), MMP-3 (also known as stromelysin 1 or EC 3.4.24.17), proteoglycanase, MMP-7 (also known as matrilysin), MMP-8 (also known as collagenase II, neutrophil collagenase, or EC 3.4.24.34), MMP-9 (also known as gelatinase B, 92kDa gelatinase, or EC 3.4.24.35), MMP-10 (also known as stromelysin 2 or EC 3.4.24.22), MMP-11 ~~[[1 I]]~~ (also known as stromelysin 3), MMP-12 (also known as metalloelastase, human macrophage elastase or HME), MMP- 13 (also known as collagenase 111), and MMP- 14 (also known as MT1-MMP or membrane MMP). *See, generally*, Woessner, J.F., "The Matrix Metalloprotease Family" in *Matrix Metalloproteinases*, pp.1-14 (Edited by Parks, W.C. & Mecham, R.P., Academic Press, San Diego, CA 1998).

Paragraph 8 on page 3 has been amended in the following manner:

[8] Inhibiting TNF (and related compounds) production and action is an important clinical disease treatment. Matrix metalloproteinase inhibition is one mechanism that can be used. MMP (*e.g.*, collagenase, stromelysin, and gelatinase) inhibitors, for example, have been reported to inhibit TNF- α release. *See, e.g.*, Gearing et al., *Nature*, 370, ~~[[376,]]~~ 555-557 (1994). *See also*, McGeehan et al. ~~*See also*, *Nature* [[376]],~~ 370, 558-561 (1994). MMP inhibitors also have been reported to inhibit TNF- α convertase, a metalloproteinase involved in forming active TNF- α . *See, e.g.*, WIPO Int'l Pub. No. WO 94/24140. *See also*, WIPO Int'l Pub. No. WO 94/02466. *See also*, WIPO Int'l Pub. No. WO 97/20824.

Paragraph 13 on page 4 has been amended in the following manner:

[13] A wide variety of thiol compounds have been reported to inhibit MMPs. *See, e.g.*, ~~W095/12389~~ WO 95/13289. *See also*, ~~[[W0]]~~ WO 96/11209. *See also*, U.S. Patent No. 4,595,700. *See also*, U.S. Patent No. 6,013,649.

Paragraph 14 on page 4 has been amended in the following manner:

[14] A wide variety of hydroxamic acid compounds also have been reported to inhibit MMPs. Such compounds reportedly include hydroxamic acids having a carbon backbone. *See, e.g.,* WIPO Int'l Pub. No. WO 95/29892. *See also,* WIPO Int'l Pub. No. WO 97/24117. *See also,* WIPO Int'l Pub. No. WO 97/49679. *See also,* European Patent No. EP 0 780 386. Such compounds also reportedly include hydroxamic acids having peptidyl backbones or peptidomimetic backbones. *See, e.g.,* WIPO Int'l Pub. No. WO 90/05719. *See also,* WIPO Int'l Pub. No. WO 93/20047. *See also,* WIPO Int'l Pub. No. WO 95/09841. *See also,* WIPO Int'l Pub. No. WO 96/06074. *See also,* Schwartz et al., *Progr. Med. Chem.*, 29:271-334(1992). *See also,* Rasmussen et al., *Pharmacol Ther.*, 75(1): 69-75 (1997). *See also,* Denis et al., *Invest New Drugs*, 15 [(3)]: 175-185 (1997). Various piperazinylsulfonylmethyl hydroxamic acids and piperidinylsulfonylmethyl hydroxamic acids have additionally been reported to inhibit MMPs. *See,* WIPO Int'l Pub. No. WO 00/46221. And various aromatic sulfone hydroxamic acids have been reported to inhibit MMPs. *See,* WIPO Int'l Pub. No. WO 99/25687. *See also,* WIPO Int'l Pub. No. WO 00/50396. *See also,* WIPO Int'l Pub. No. WO 00/69821.

Paragraph 15 on page 5 has been amended in the following manner:

[15] It is often advantageous for an MMP inhibitor drug to target a certain MMP(s) over another MMP(s). For example, it is typically preferred to inhibit MMP-2, MMP-3, MMP-9, and/or MMP-13 (particularly MMP-13) when treating cancer, inhibiting of metastasis, and inhibiting angiogenesis. It also is typically preferred to inhibit MMP-13 when treating osteoarthritis. *See, e.g.,* Mitchell et al., *J Clin. Invest.*, 97(3):761-768 (1996). *See also,* Reboul et al., *J Clin. Invest.*, 97(9):2011-2019 (1996). Normally, however, it is preferred to use a drug that has little or no inhibitory effect on MMP-1 and MMP-14. This preference stems from the fact that both MMP-1 and MMP-14 are involved in several homeostatic processes, and inhibition of MMP-1 and/or MMP-14 consequently tends to interfere with such processes.

Paragraph 20 on page 6 has been amended in the following manner:

[20] Various hydroxamic acid compounds have been reported to inhibit aggrecanase-1. Such compounds include, for example, those described in European Patent Application Publ. No.

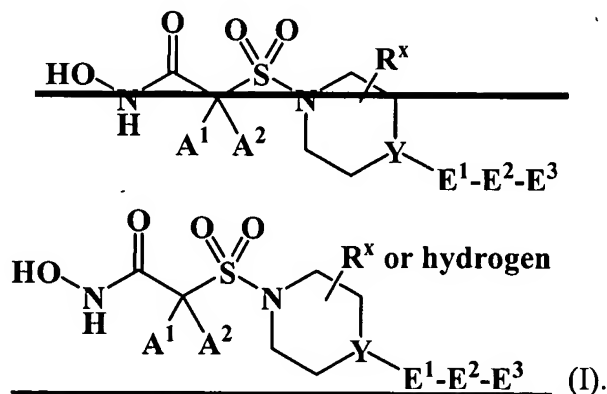
EP 1 081 137 A1. Such compounds also include, for example, those described in WIPO PCT Int'l Publ. No. WO 99/09000 ~~00/09000~~. Such compounds further include, for example, those described in WIPO PCT Int'l Publ. No. WO 00/59874.

Paragraph 22 on page 7 has been amended in the following manner:

[22] This invention is directed to, for example, compounds and salts thereof that inhibit protease activity, particularly compounds that inhibit MMP-2, MMP-9, MMP- 13, and/or aggrecanase, while generally exhibiting relatively little or no inhibition against MMP-1 and MMP-14 activity. This invention also is directed to, for example, a method for inhibiting protease activity, particularly pathological MMP activity. Such a method is particularly suitable to be used with mammals, such as humans, other primates (*e.g.*, monkeys, chimpanzees. etc.), companion animals (*e.g.*, dogs, cats, horses, ~~[[.]]~~ etc.), farm animals (*e.g.*, goats, sheep, pigs, cattle, etc.), laboratory animals (*e.g.*, mice, rats, etc.), and wild and zoo animals (*e.g.*, wolves, bears, deer, etc.).

Paragraph 23 on page 7 has been amended in the following manner:

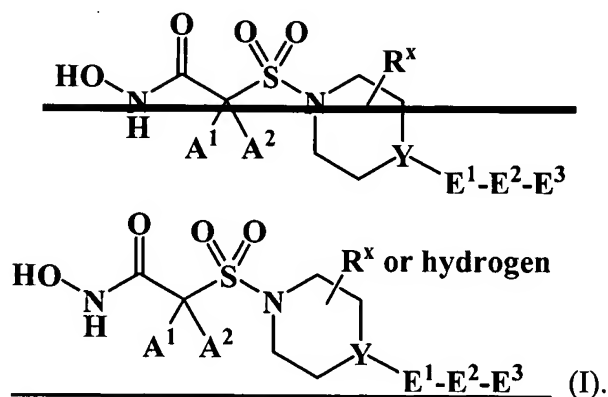
[23] Briefly, therefore, this invention is directed, in part, to a compound that corresponds in structure to Formula I (or a salt thereof):



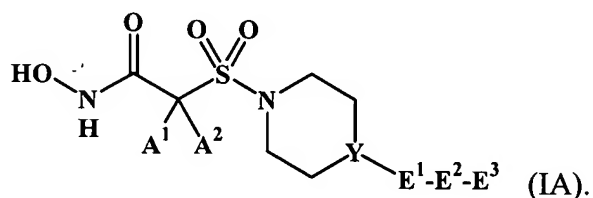
Generally, Y, A¹, A², E¹, E², and E³ are defined as follows:

Paragraph 47 on page 13 has been amended in the following manner:

[47] As noted above, the compounds of this invention generally have a structure corresponding to Formula I:



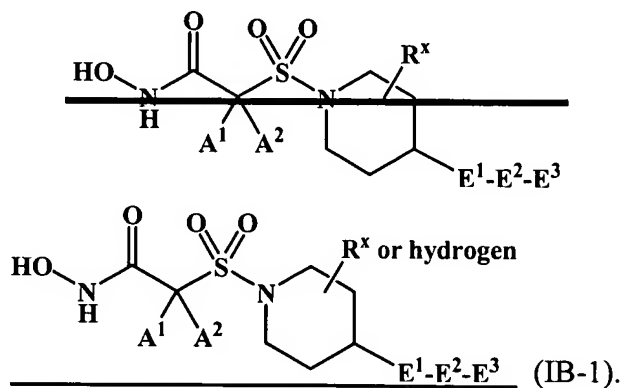
In many preferred embodiments, such compounds generally correspond in structure to the following formula (IA):



In these formulas, Y, A¹, A², E¹, E², E³, and R^x are defined as follows:

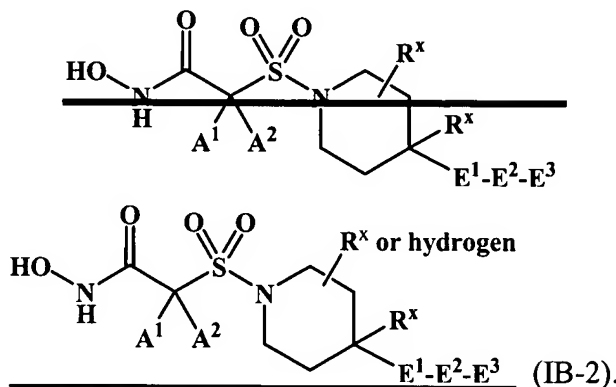
Paragraph 49 on page 14 has been amended in the following manner:

[49] If Y is carbon bonded to hydrogen, the compound corresponds in structure to Formula (IB-1):

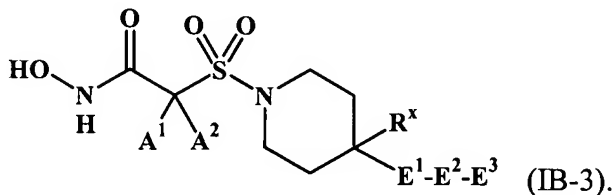


Paragraph 50 on page 14 has been amended in the following manner:

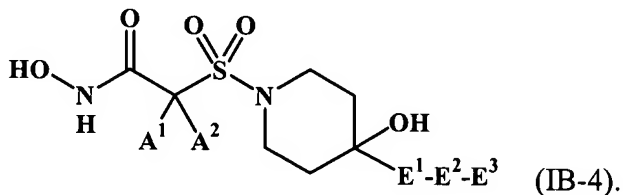
[50] If, on the other hand, Y is bonded to an R^x substituent, the compound corresponds in structure to Formula (IB-2):



In many such embodiments, the piperidine bridging the sulfonyl and E^1 is preferably not otherwise substituted with an R^x substituent. In that instance, the compound corresponds in structure to Formula (IB-3):

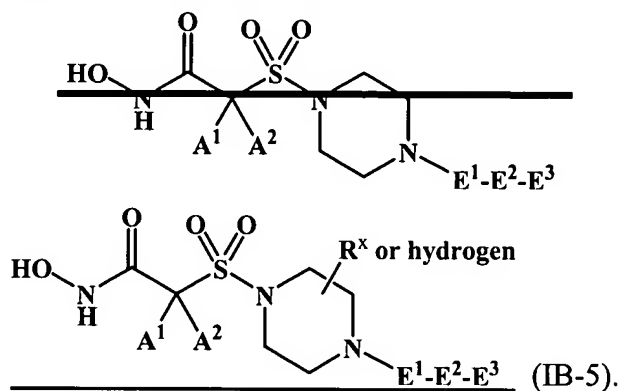


In some such embodiments, Y is preferably carbon bonded to halogen. In other such embodiments, Y is preferably carbon bonded to hydroxy. In those embodiments, the compound corresponds in structure to Formula (IB-4)



Paragraph 51 bridging pages 14 and 15 has been amended in the following manner:

[51] If Y is nitrogen, the compound corresponds in structure to Formula (IB-5):



Paragraph 91 bridging pages 26 and 27 has been amended in the following manner:

[91] In some preferred embodiments, E¹ is pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, tetrahydropyranyl, dihydrofuranyl, tetrahydrofuranyl, thienyl, dihydrothienyl, tetrahydrothienyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, oxazolidinyl, isoxazolidinyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazolyl, oxatriazolyl, dioxazolyl, oxathiolyl, oxathiolanyl, pyranyl, dihydropyranyl, pyridinyl, piperidinyl, diazinyl, piperazinyl, triazinyl, oxazinyl, isoxazinyl, oxathiazinyl, oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl, diazepinyl, indolizinyl, pyridinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, tetrahydroisoquinolinyl, carbazolyl, xanthenyl, or acridinyl. Each such substituent is (if substitutable at one or more positions other than the position occupied by -E²-E³) optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, oxo, amino, mono-alkylamino, di-alkylamino, nitro, nitroso, alkyl, alkoxy, alkoxyalkyl, and alkylthio. The optional alkyl, alkoxy, alkoxyalkyl, alkylthio, mono-alkylamino, and di-alkylamino substituents are, in turn, optionally substituted with one or more substituents

independently selected from the group consisting of halogen, hydroxy, cyano, carboxy, thiol, sulfo, nitro, nitroso, thioxo, and imino.

Paragraph 92 on page 27 has been amended in the following manner:

[92] In some preferred embodiments, E¹ is pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, tetrahydropyranyl, dihydrofuranyl, tetrahydrofuranyl, thienyl, dihydrothienyl, tetrahydrothienyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazoliny, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxazolidinyl, isoxazolidinyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazolyl, oxatriazolyl, oxathioly, oxathiolanyl, pyranyl, dihydropyranyl, pyridinyl, piperidinyl, piperazinyl, triazinyl, oxazinyl, morpholinyl, azepinyl, diazepinyl, indoliziny, pyrindinyl, pyranopyrrolyl, 4H-quinoliziny, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, tetrahydroisoquinoliny, carbazolyl, xanthenyl, or acridinyl. Each such substituent is (if substitutable at one or more positions other than the position occupied by -E²-E³) optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, oxo, amino, mono-alkylamino, di-alkylamino, nitro, nitroso, alkyl, alkoxy, alkoxyalkyl, and alkylthio. The optional alkyl, alkoxy, alkoxyalkyl, alkylthio, mono-alkylamino, and di-alkylamino substituents are, in turn, optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, cyano, carboxy, thiol, sulfo, nitro, nitroso, thioxo, and imino.

Paragraph 97 on page 28 has been amended in the following manner:

[97] In some preferred embodiments, E¹ is pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrrolyl, isopyrrolyl, imidazolyl, isoimidazolyl, pyrazolyl, triazolyl, dithiolyl, oxathioly, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiodiazolyl, oxathiazolyl, oxadiazolyl, dioxazolyl, oxathioly, pyranyl, pyridinyl, diazinyl, triazinyl, tetrazolyl, oxazinyl, isoxazinyl,

oxathiazinyl, oxadiazinyl, azepinyl, oxepinyl, thiepinyl, or diazepinyl. Each such substituent (if substitutable at one or more positions other than the position occupied by $-E^2-E^3$) is, in turn, optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, amino, mono-alkylamino, di-alkylamino, nitro, nitroso, alkyl, alkoxy, alkoxyalkyl, and alkylthio. The optional alkyl, alkoxy, alkoxyalkyl, alkylthio, mono-alkylamino, and di-alkylamino substituents are, in turn, optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, cyano, carboxy, thiol, sulfo, nitro, nitroso, thioxo, and imino.

Paragraph 98 on page 29 has been amended in the following manner:

[98] In some preferred embodiments, E^1 is pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrrolyl, isopyrrolyl, imidazolyl, isoimidazolyl, pyrazolyl, triazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiodiazolyl, oxathiazolyl, oxadiazolyl, dioxazolyl, oxathiolyl, pyranyl, pyridinyl, diazinyl, triazinyl, tetrazolyl, oxazinyl, isoxazinyl, oxathiazinyl, oxadiazinyl, azepinyl, oxepinyl, thiepinyl, or diazepinyl.

Paragraph 99 on page 29 has been amended in the following manner:

[99] In some preferred embodiments, E^1 is pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiodiazolyl, oxathiazolyl, oxadiazolyl, oxathiolyl, pyranyl, pyridinyl, triazinyl, tetrazolyl, oxazinyl, azepinyl, or diazepinyl. Each such substituent is optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, amino, mono-alkylamino, di-alkylamino, nitro, nitroso, alkyl, alkoxy, alkoxyalkyl, and alkylthio. Such optional substituents, in turn, are optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, cyano, carboxy, thiol, sulfo, nitro, nitroso, thioxo, and imino.

Paragraph 100 on page 29 has been amended in the following manner:

[100] In some preferred embodiments, E^1 is pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl,

isothiazolyl, thiodiazolyl, oxathiazolyl, oxadiazolyl, oxathiolyl, pyranyl, pyridinyl, triazinyl, tetrazolyl, oxazinyl, azepinyl, or diazepinyl.

Paragraph 184 bridging pages 44 and 45 has been amended in the following manner:

[184] In some preferred embodiments, any heterocyclyl of R^x is selected from the group consisting of pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, tetrahydropyranyl, dihydrofuranyl, tetrahydrofuranyl, thienyl, dihydrothienyl, tetrahydrothienyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazoliny, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, oxazolidinyl, isoxazolidinyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazolyl, oxatriazolyl, dioxazolyl, oxathiolyl, oxathiolanyl, pyranyl, dihydropyranyl, pyridinyl, piperidinyl, diazinyl, piperazinyl, triazinyl, oxazinyl, isoxazinyl, oxathiazinyl, oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl, diazepinyl, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, tetrahydroisoquinolinyl, carbazolyl, xanthenyl, and acridinyl.

Paragraph 185 on page 45 has been amended in the following manner:

[185] In some preferred embodiments, any heterocyclyl of R^x is selected from the group consisting of pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, tetrahydropyranyl, dihydrofuranyl, tetrahydrofuranyl, thienyl, dihydrothienyl, tetrahydrothienyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazoliny, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxazolidinyl, isoxazolidinyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazolyl, oxatriazolyl, oxathiolyl, oxathiolanyl, pyranyl, dihydropyranyl, pyridinyl, piperidinyl, piperazinyl, triazinyl, oxazinyl, morpholinyl, azepinyl, diazepinyl, indolizinyl, pyrindinyl,

pyranopyrrolyl, 4H-quinoliziny, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, tetrahydroisoquinoliny, carbazolyl, xanthenyl, and acridinyl.

Paragraph 229 bridging pages 56 and 57 has been amended in the following manner:

[229] In some preferred embodiments, any heterocyclyl of any R^a substituent is independently selected from the group consisting of pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, tetrahydropyranyl, dihydrofuranyl, tetrahydrofuranyl, thienyl, dihydrothienyl, tetrahydrothienyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazoliny, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, oxazolidinyl, isoxazolidinyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazolyl, oxatriazolyl, dioxazolyl, oxathiolyl, oxathiolanyl, pyranyl, dihydropyranyl, pyridinyl, piperidinyl, diazinyl, piperazinyl, triazinyl, oxazinyl, isoxazinyl, oxathiazinyl, oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl, diazepinyl, indoliziny, pyrindinyl, pyranopyrrolyl, 4H-quinoliziny, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, tetrahydroisoquinoliny, carbazolyl, xanthenyl, and acridinyl.

Paragraph 230 on page 57 has been amended in the following manner:

[230] In some preferred embodiments, any heterocyclyl of any R^a substituent is independently selected from the group consisting of pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, tetrahydropyranyl, dihydrofuranyl, tetrahydrofuranyl, thienyl, dihydrothienyl, tetrahydrothienyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazoliny, imidazolidinyl, pyrazolyl,

pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxazolidinyl, isoxazolidinyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazolyl, oxatriazolyl, oxathiolyl, oxathiolanyl, pyranyl, dihydropyranyl, pyridinyl, piperidinyl, piperazinyl, triazinyl, oxazinyl, morpholinyl, azepinyl, diazepinyl, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiaazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, tetrahydroisoquinolinyl, carbazolyl, xanthenyl, and acridinyl.

Paragraph 231 bridging pages 57 and 58 has been amended in the following manner:

[231] In some preferred embodiments, any heterocyclyl of R^a and R^x is independently selected from the group consisting of pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, tetrahydropyranyl, dihydrofuranyl, tetrahydrofuranyl, thienyl, dihydrothienyl, tetrahydrothienyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazoliny, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, oxazolidinyl, isoxazolidinyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazolyl, oxatriazolyl, dioxazolyl, oxathiolyl, oxathiolanyl, pyranyl, dihydropyranyl, pyridinyl, piperidinyl, diazinyl, piperazinyl, triazinyl, oxazinyl, isoxazinyl, oxathiazinyl, oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl, diazepinyl, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiaazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, tetrahydroisoquinolinyl, carbazolyl, xanthenyl, and acridinyl.

Paragraph 232 on page 58 has been amended in the following manner:

[232] In some preferred embodiments, any heterocyclyl of R^a and R^x is independently selected from the group consisting of pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, tetrahydropyranyl, dihydrofuranyl, tetrahydrofuranyl, thienyl, dihydrothienyl, tetrahydrothienyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxazolidinyl, isoxazolidinyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazolyl, oxatriazolyl, oxathiyl, oxathiolanyl, pyranyl, dihydropyranyl, pyridinyl, piperidinyl, piperazinyl, triazinyl, oxazinyl, morpholinyl, azepinyl, diazepinyl, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, tetrahydroisoquinolyl, carbazolyl, xanthenyl, and acridinyl.

Paragraph 246 on page 61 has been amended in the following manner:

[246] In some particularly preferred embodiments, the heteroaryl of E¹ is pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiodiazolyl, oxathiazolyl, oxadiazolyl, oxathiyl, pyranyl, pyridinyl, triazinyl, tetrazolyl, oxazinyl, azepinyl, or diazepinyl. Each such substituent (if substitutable at one or more positions other than the position occupied by -E²-E³) is, in turn, optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, amino, mono-alkylamino, di-alkylamino, nitro, nitroso, alkyl, alkoxy, alkoxyalkyl, and alkylthio. The optional alkyl, alkoxy, alkoxyalkyl, alkylthio, mono-alkylamino, and di-alkylamino substituents are, in turn, optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, cyano, carboxy, thiol, sulfo, nitro, nitroso, thioxo, and imino.

Paragraph 248 on page 61 has been amended in the following manner:

[248] In some particularly preferred embodiments, E¹ is pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrrolyl, isopyrrolyl, imidazolyl, isoimidazolyl, pyrazolyl, triazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiodiazolyl, oxathiazolyl, oxadiazolyl, dioxazolyl, oxathiolyl, pyranyl, pyridinyl, diazinyl, triazinyl, tetrazolyl, oxazinyl, isoxazinyl, oxathiazinyl, oxadiazinyl, azepinyl, oxepinyl, thiepinyl, or diazepinyl.

Paragraph 249 bridging pages 61 and 62 has been amended in the following manner:

[249] In some particularly preferred embodiments, E¹ is pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiodiazolyl, oxathiazolyl, oxadiazolyl, oxathiolyl, pyranyl, pyridinyl, triazinyl, tetrazolyl, oxazinyl, azepinyl, or diazepinyl.

Paragraph 275 bridging pages 69 and 70 has been amended in the following manner:

[275] In some particularly preferred embodiments, E¹ is pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, tetrahydropyranyl, dihydrofuranyl, tetrahydrofuranyl, thienyl, dihydrothienyl, tetrahydrothienyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, oxazolidinyl, isoxazolidinyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazolyl, oxatriazolyl, dioxazolyl, oxathiolyl, oxathiolanyl, pyranyl, dihydropyranyl, pyridinyl, piperidinyl, diazinyl, piperazinyl, triazinyl, oxazinyl, isoxazinyl, oxathiazinyl, oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl, diazepinyl, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, tetrahydroisoquinolinyl, carbazolyl, xanthenyl, or acridinyl. Each

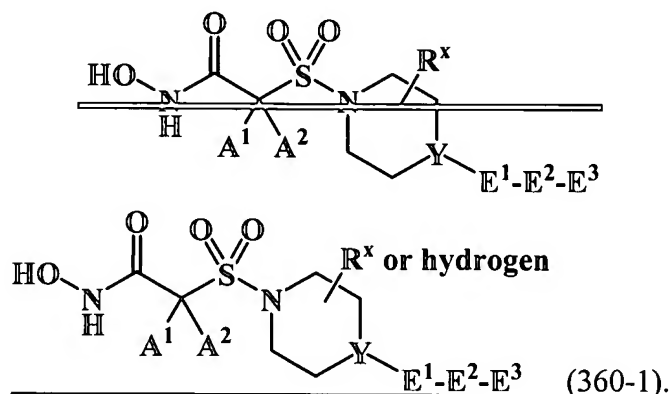
such substituent is (if substitutable at one or more positions other than the position occupied by $-E^2-E^3$) optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, oxo, amino, mono-alkylamino, di-alkylamino, nitro, nitroso, alkyl, alkoxy, alkoxyalkyl, and alkylthio. The optional alkyl, alkoxy, alkoxyalkyl, alkylthio, mono-alkylamino, and di-alkylamino substituents are, in turn, optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, cyano, carboxy, thiol, sulfo, nitro, nitroso, thioxo, and imino.

Paragraph 276 bridging pages 70 and 71 has been amended in the following manner:

[276] In some particularly preferred embodiments, E^1 is pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, tetrahydropyranyl, dihydrofuranyl, tetrahydrofuranyl, thienyl, dihydrothienyl, tetrahydrothienyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolanyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxazolidinyl, isoxazolidinyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazolyl, oxatriazolyl, oxathieryl, oxathiolanyl, pyranyl, dihydropyranyl, pyridinyl, piperidinyl, piperazinyl, triazinyl, oxazinyl, morpholinyl, azepinyl, diazepinyl, indolizinyl, pyridinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, tetrahydroisoquinolinyl, carbazolyl, xanthenyl, or acridinyl. Each such substituent is (if substitutable at one or more positions other than the position occupied by $-E^2-E^3$) optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, oxo, amino, mono-alkylamino, di-alkylamino, nitro, nitroso, alkyl, alkoxy, alkoxyalkyl, and alkylthio. The optional alkyl, alkoxy, alkoxyalkyl, alkylthio, mono-alkylamino, and di-alkylamino substituents are, in turn, optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, cyano, carboxy, thiol, sulfo, nitro, nitroso, thioxo, and imino.

Paragraph 629 on page 186 has been amended in the following manner:

[629] In some preferred embodiments, the compounds correspond in structure to Formula (360-1):



In these embodiments:

The header at line 1 on page 189 has been amended in the following manner:

A-2. Preferred MMP Selectivities

Paragraph 654 on page 191 has been amended in the following manner:

[654] In some particularly preferred embodiments, the hydroxamic acid compound or salt preferably has K_i 's against all of MMP-2, MMP-9, and MMP-13 [[3]] that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i 's against both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when treating, for example, cancer, a cardiovascular condition, arthritis, or an ophthalmologic condition.

Paragraph 665 bridging pages 193 and 194 has been amended in the following manner:

[665] In some particularly preferred embodiments, the hydroxamic acid compound or salt preferably has IC_{50} values against all of MMP-2, MMP-9, and MMP-13 [[3]] that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more

preferably no greater than about 0.00001) times its IC₅₀ values against both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when treating, for example, cancer, a cardiovascular condition, arthritis, or an ophthalmologic condition.

Paragraph 668 bridging pages 194 and 195 has been amended in the following manner:

[668] Pharmaceutically-acceptable acid addition salts of the compounds of this invention may be prepared from an inorganic or organic acid. Examples of suitable inorganic acids include hydrochloric, hydrobromic acid, ~~hydroionic~~ hydroiodic, nitric, carbonic, sulfuric, and phosphoric acid. Suitable organic acids generally include, for example, aliphatic, cycloaliphatic, aromatic, araliphatic, ~~heterocyclic~~ heterocyclic, ~~carboxylic~~ carboxylic, and sulfonic classes of organic acids. Specific examples of suitable organic acids include acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate, digluconate, lactate, malate, tartaric acid, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilic acid, mesylate, stearate, salicylate, p-hydroxybenzoate, phenylacetate, mandelate, embonate (pamoate), ~~methanesulfonate~~, ethanesulfonate, benzenesulfonate, pantothenate, ~~toluenesulfonate~~, 2-hydroxyethanesulfonate, ~~sufanilate~~ sulfanilate, cyclohexylaminosulfonate, algenic acid, ~~[[b-]]~~ β-hydroxybutyric acid, galactarate, galacturonate, adipate, alginate, ~~bisulfate~~, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, dodecylsulfate, glycoheptanoate, glycerophosphate, ~~hemisulfate~~, heptanoate, hexanoate, nicotinate, 2-naphthalesulfonate, oxalate, palmoate, pectinate, ~~persulfate~~, 3-phenylpropionate, picrate, pivalate, thiocyanate, tosylate, and undecanoate.

Paragraph 669 on page 195 has been amended in the following manner:

[669] Pharmaceutically-acceptable base addition salts of the compounds of this invention include, for example, metallic salts and organic salts. Preferred metallic salts include alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts, and other ~~physiological~~ physiologically acceptable metal salts. Such salts may be made from aluminum, calcium, lithium, magnesium, potassium, sodium, and zinc. Preferred organic salts can be made from ~~tertiary amines and quaternary amine salts~~, such as tromethamine, diethylamine,

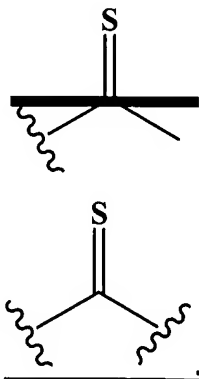
N,N'-dibenzylethylenediamine, chlorprocaine, ~~choline~~, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine. Basic nitrogen-containing groups can be quaternized with agents such as lower alkyl (C₁-C₆) halides (*e.g.*, methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides), dialkyl sulfates (*e.g.*, dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (*e.g.*, decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides), aralkyl halides (*e.g.*, benzyl and phenethyl bromides), and others.

Paragraph 686 on page 197 has been amended in the following manner:

[686] Typically, a compound (or pharmaceutically acceptable salt thereof) described in this patent is administered in an amount effective to inhibit a target MMP(s) or aggrecanase. The target MMP is/are typically MMP-2, MMP-9, and/or MMP-13, with MMP-13 often being a particularly preferred target. The preferred total daily dose of the hydroxamic acid or salt thereof (administered in single or divided doses) is typically from about 0.001 to about 100 mg/kg, more preferably from about 0.001 to about 30 mg/kg, and even more preferably from about 0.01 to about 10 mg/kg (*i.e.*, mg hydroxamic acid or salt thereof per kg body weight). Dosage unit compositions can contain such amounts or submultiples thereof to make up the daily dose. In many instances, the administration of the compound or salt will be repeated a plurality of times. Multiple doses per day typically may be used to increase the total daily dose, if desired.

Paragraph 731 on page 206 has been amended in the following manner:

[731] The term “(thiocarbonyl)” (alone or in combination with another term(s)) means a carbonyl wherein the oxygen atom has been replaced with a sulfur. Such a substituent may be depicted as -C(S)-, and also may be depicted as:



Paragraph 735 on page 207 has been amended in the following manner:

[735] The term “heterocyclyl” (alone or in combination with another term(s)) means a saturated (*i.e.*, “heterocycloalkyl”), partially saturated (*i.e.*, “heterocycloalkenyl”), or **completely unsaturated** (~~*i.e.*, “heteroaryl [”]~~) ring structure containing a total of 3 to 14 ring atoms. At least one of the ring atoms is a heteroatom (*i.e.*, oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur.

Paragraph 736 bridging pages 207 and 208 has been amended in the following manner:

[736] A heterocyclyl may be a single ring, which typically contains from 3 to 7 ring atoms, more typically from 3 to 6 ring atoms, and even more typically 5 to 6 ring atoms. Examples of single-ring heterocyclyls include furanyl, dihydrofurnayl, tetrahydrofurnayl, thiophenyl (also known as “thiofuranyl”), dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazolyl (including 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl (also known as “azoximyl”), 1,2,5-oxadiazolyl (also known as “furazanyl”), **and** **[[or]]** 1,3,4-oxadiazolyl), oxatriazolyl (including 1,2,3,4-oxatriazolyl **and** **[[or]]** 1,2,3,5-oxatriazolyl), dioxazolyl (including 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, **and** **[[or]]** 1,3,4-dioxazolyl), ~~oxathiazolyl, oxathioly~~, oxathiolanyl, pyranyl (including 1,2-pyranyl **and** **[[or]]** 1,4-pyranyl), dihydropyranyl, pyridinyl (~~also known as “azinyl”~~), piperidinyl, diazinyl (including pyridazinyl (also known as “1,2-diazinyl”), pyrimidinyl (also known as “1,3-diazinyl”), **and** **[[or]]** pyrazinyl (also known as “1,4-diazinyl”)), piperazinyl, triazinyl (including s-triazinyl (also known as “1,3,5-triazinyl”), as-triazinyl (also known 1,2,4-triazinyl), and v-triazinyl (also known as “1,2,3-triazinyl”)), oxazinyl (including 1,2,3-oxazinyl, 1,3,2-oxazinyl, 1,3,6-oxazinyl (also known as “pentoxazolyl”), 1,2,6-oxazinyl, **and** **[[or]]** 1,4-oxazinyl), isoxazinyl (including o-isoxazinyl **and** **[[or]]** p-isoxazinyl), oxazolidinyl, isoxazolidinyl, oxathiazinyl (including 1,2,5-oxathiazinyl **and** **[[or]]** 1,2,6-oxathiazinyl),

oxadiazinyl (including 1,4,2-oxadiazinyl and ~~[[or]]~~ 1,3,5,2-oxadiazinyl), morpholinyl, azepinyl, oxepinyl, thiepinyl, and diazepinyl.

Paragraph 737 on page 208 has been amended in the following manner:

[737] A heterocyclyl alternatively may be 2 or 3 rings fused together, such as, for example, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, ~~naphthyridinyl~~, pyridopyridinyl (including pyrido[3,4-b]-pyridinyl, pyrido[3,2-b]-pyridinyl, ~~[[or]]~~ pyrido[4,3-b]-pyridinyl, and naphthyridinyl), and pteridinyl. Other examples of fused-ring heterocyclyls include benzo-fused heterocyclyls, such as indolyl, isoindolyl (~~also known as “isobenzazolyl” or “pseudoisoindolyl”~~), indoleninyl (also known as “pseudoindolyl”), isoindazolyl (also known as “benzpyrazolyl”), benzazinyl (including quinolinyl (also known as “1-benzazinyl”) and ~~[[or]]~~ isoquinolinyl (also known as “2-benzazinyl”)), phthalazinyl, quinoxalinyl, ~~quinazolinyl~~, benzodiazinyl (including cinnolinyl (also known as “1,2-benzodiazinyl”) and ~~[[or]]~~ quinazolinyl (also known as “1,3-benzodiazinyl”)), benzopyranyl (including chromenyl and isochromenyl ~~“chromanyl” or “isochromanyl”~~), benzothiopyranyl (also known as thiochromenyl ~~“thiochromanyl”~~), benzoxazolyl, indoxazinyl (also known as “benzisoxazolyl”), anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl (also known as “coumaronyl”), isobenzofuranyl, benzothieryl (also known as “benzothiophenyl”, “thionaphthenyl”, or “benzothiofuranyl”), isobenzothieryl (also known as “isobenzothiophenyl”, “isothionaphthenyl”, or “isobenzothiofuranyl”), benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl (including 1,3,2-benzoxazinyl[[]], 1,4,2-benzoxazinyl[[]], 2,3,1-benzoxazinyl[[]], and ~~[[or]]~~ 3,1,4-benzoxazinyl[[]]), benzisoxazinyl (including 1,2-benzisoxazinyl and ~~[[or]]~~ 1,4-benzisoxazinyl), tetrahydroisoquinolinyl[[]], carbazolyl, xanthenyl, and acridinyl.

Paragraph 738 bridging pages 208 and 209 has been amended in the following manner:

[738] The term 2-fused-ring ~~“2-fused ring”~~ heterocyclyl (alone or in combination with another term(s)) means a saturated, partially saturated, or aryl heterocyclyl containing 2 fused rings. Examples of 2-fused-ring heterocyclyls include indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, ~~naphthyridinyl~~, pyridopyridinyl, pteridinyl, indolyl, isoindolyl,

indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, and tetrahydroisoquinolinyl.

Paragraph 739 on page 209 has been amended in the following manner:

[739] The term “heteroaryl” (alone or in combination with another term(s)) means an aromatic heterocyclyl containing from 5 to 14 ring atoms. A heteroaryl may be a single ring or 2 or 3 fused rings. Examples of heteroaryl substituents include 6-membered ring substituents such as ~~pyridyl, pyrazyl, pyridinyl, pyrazinyl,~~ pyrimidinyl, ~~[[and]] pyridazinyl, and 1,3,5-, 1,2,4-, and 1,2,3-triazinyl;~~ 5-membered ring substituents such as ~~1,3,5-, 1,2,4- or 1,2,3-triazinyl, imidazolyl~~ imidazolyl, furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 1,2,4-, 1,2,5-, and ~~[[or]] 1,3,4-oxadiazolyl, and isothiazolyl;~~ 6/5-membered fused ring substituents such as benzothiofuranyl, isobenzothiofuranyl, benzisoxazolyl, benzoxazolyl, purinyl, and anthranilyl; and 6/6-membered fused rings such as ~~1,2-, 1,4-, 2,3- and 2,1-benzopyronyl,~~ quinolinyl, isoquinolinyl, cinnolinyl, and quinazolinyl, ~~and 1,4-benzoxazinyl.~~

Paragraph 741 bridging pages 209 and 211 has been amended in the following manner:

[741] An aryl or heteroaryl can optionally be substituted with, for example, one or more substituents independently selected from the group consisting of halogen, -OH, -CN, -NO₂, -SH, -C(O)-OH, amino, aminocarbonyl, aminoalkyl, alkyl, alkylthio, carboxyalkylthio, alkylcarbonyl, alkylcarbonyloxy, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkoxy, alkoxyalkylthio, alkoxycarbonylalkylthio, carboxyalkoxy, alkoxycarbonylalkoxy, carbocyclyl, carbocyclylalkyl, carbocyclylloxy, carbocyclylthio, carbocyclylalkylthio, carbocyclylamino, carbocyclylalkylamino, carbocyclylcarbonylamino, carbocyclylcarbonyl, carbocyclylalkyl, ~~carbonyl,~~ carbocyclylcarbonyloxy, carbocyclylloxycarbonyl, carbocyclylalkoxycarbonyl, carbocyclylloxycarbocyclyl, carbocyclylthioalkylthiocarbocyclyl, carbocyclylthioalkoxycarbocyclyl, carbocyclylloxyalkylthiocarbocyclyl, heterocyclyl, heterocyclylalkyl, heterocyclylloxy, heterocyclylthio, heterocyclylalkylthio, heterocyclylamino,

heterocyclylalkylamino, heterocyclylcarbonylamino, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, heterocyclylloxycarbonyl, heterocyclylcarbonyloxy, heterocyclylalkoxycarbonyl, heterocyclylalkoxyheterocyclyl, heterocyclylthioalkylthioheterocyclyl, heterocyclylthioalkoxyheterocyclyl, and heterocyclylalkylthioheterocyclyl. More typically, an aryl or heteroaryl may, for example, optionally be substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -CN, -NO₂, -SH, -C(O)-OH, amino, aminocarbonyl, amino-C₁-C₆-alkyl, C₁-C₆-alkyl, C₁-C₆-alkylthio, carboxy-C₁-C₆-alkylthio, C₁-C₆-alkylcarbonyl, C₁-C₆-alkylcarbonyloxy, C₁-C₆-alkoxy, C₁-C₆-alkoxy-C₁-C₆-alkyl, C₁-C₆-alkoxycarbonyl, C₁-C₆-alkoxycarbonyl-C₁-C₆-alkoxy, C₁-C₆-alkoxy-C₁-C₆-alkylthio, C₁-C₆-alkoxycarbonyl-C₁-C₆-alkylthio, carboxy-C₁-C₆-alkoxy, C₁-C₆-alkoxycarbonyl-C₁-C₆-alkoxy, aryl, aryl-C₁-C₆-alkyl, aryloxy, arylthio, aryl-C₁-C₆-alkylthio, arylamino, aryl-C₁-C₆-alkylamino, arylcarbonylamino, arylcarbonyl, aryl-C₁-C₆-alkylcarbonyl, arylcarbonyloxy, aryloxycarbonyl, aryl-C₁-C₆-alkoxycarbonyl, aryloxy-C₁-C₆-alkoxyaryl, arylthio-C₁-C₆-alkylthioaryl, arylthio-C₁-C₆-alkoxyaryl, aryloxy-C₁-C₆-alkylthioaryl, cycloalkyl, cycloalkyl-C₁-C₆-alkyl, cycloalkyloxy, cycloalkylthio, cycloalkyl-C₁-C₆-alkylthio, cycloalkylamino, cycloalkyl-C₁-C₆-alkylamino, cycloalkylcarbonylamino, cycloalkylcarbonyl, cycloalkyl-C₁-C₆-alkylcarbonyl, cycloalkylcarbonyloxy, cycloalkyloxycarbonyl, cycloalkyl-C₁-C₆-alkoxycarbonyl, heteroaryl, heteroaryl-C₁-C₆-alkyl, heteroaryloxy, heteroarylthio, heteroaryl-C₁-C₆-alkylthio, heteroarylamino, heteroaryl-C₁-C₆-alkylamino, heteroarylcarbonylamino, heteroarylcarbonyl, heteroaryl-C₁-C₆-alkylcarbonyl, heteroaryloxycarbonyl, heteroarylcarbonyloxy, and heteroaryl-C₁-C₆-alkoxycarbonyl. Here, one or more hydrogen bound to a carbon in any such substituent may, for example, optionally be replaced with halogen. In addition, the cycloalkyl, aryl, and heteroaryl are typically single-ring substituents containing 3 to 6 ring atoms, and more typically 5 or 6 ring atoms.

Paragraph 925 on page 280 has been amended in the following manner:

[925] **Part E.** The THP-hydroxamate of **Part D** (1.1 g, 2.0 mmol) was dissolved in methanol (50 mL). Acetyl chloride (ca. 5 mL) was added slowly. After 10 min, the solution was concentrated. The solid was triturated with ether and dried in a vacuum oven at 40°C, affording

849 mg of the title **hydroxamic acid hydroxamate** (95%). MS MH⁺ calc'd. for C₂₁H₃₂FN₃O₅S 458.2125, found 458.2143. Anal. Calc'd for C₂₁H₃₂FN₃O₅S(1HCl): C, 51.06; H, 6.73; N, 8.51. Obs.: C, 50.77; H, 7.57; N, 8.52.

Paragraph 970 on page 297 has been amended in the following manner:

[297] Human recombinant MMP-1, MMP-2, MMP-9, MMP-13, and MMP-14 were used in this assay. All enzymes were prepared in Assignee's laboratories following usual laboratory procedures. Protocols for the preparation and use of these enzymes are available in the scientific literature. *See, e.g., Enzyme Nomenclature* (Academic Press, San Diego, CA, 1992) (and the citations therein). *See also*, [[Frijel] **Freije**, et al., *J Biol. Chem.*, [[26]] **269**(24), 16766-**16773** [[73]] (1994).

Paragraph 974 on page 297 has been amended in the following manner:

[974] The MMP-13 was obtained as a proenzyme from a full-length cDNA clone using baculovirus, as described by V.A. Luckow, "Insect Cell Expression Technology," *Protein Engineering: Principles and Practice*, pp. 183-218 (edited by J.L. Cleland et al., Wiley-Liss, Inc., 1996). The expressed proenzyme was first purified over a heparin agarose column, and then over a chelating zinc chloride column. The proenzyme was then activated by APMA for use in the assay. Further details on baculovirus expression systems may be found in, for example, Luckow et al., *J. Virol.*, 67(**8**), 4566-79 (1993). *See also*, O'Reilly et al, *Baculovirus Expression Vectors: A Laboratory Manual* (W.H. Freeman and Co., New York, NY, 1992). *See also*, King et al., *The Baculovirus Expression System: A Laboratory Guide* (Chapman & Hall, London, England, 1992).

Paragraph 1350 on page 602 has been amended in the following manner:

[1350] The study of angiogenesis depends on a reliable and reproducible model for the stimulation and inhibition of a neovascular response. The corneal micropocket assay provides such a model of angiogenesis in the cornea of a mouse. *See*, **Kenyon, B.M, et al., "A Model of Angiogenesis in the Mouse Cornea"** ; ~~Kenyon, B.M, et al.~~, *Investigative Ophthalmology & Visual Science*, ~~July 1996~~ **pp. 1625-1632**, Vol. 37, No. 8 (**July 1996**).

Paragraph 1398 bridging pages 607 and 609 has been amended in the following manner:

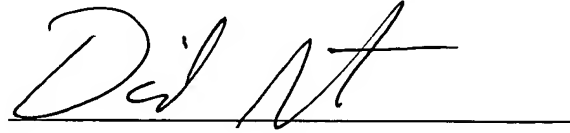
[1398] Another assay for measuring aggrecanase inhibition is reported in WIPO Int'l Publ. No. WO 00/59874. That assay reportedly uses active aggrecanase accumulated in media from stimulated bovine cartilage (BNC) or related cartilage sources and purified cartilage aggrecan monomer or a fragment thereof as a substrate. Aggrecanase is generated by stimulation of cartilage slices with interleukin-1 (IL-1), tumor necrosis factor alpha (TNF- α), or other stimuli. To accumulate BNC aggrecanase in culture media, cartilage reportedly is first depleted of endogenous aggrecan by stimulation with 500 ng/ml human recombinant IL- β for 6 days with media changes every 2 days. Cartilage is then stimulated for an additional 8 days without media change to allow accumulation of soluble, active aggrecanase in the culture media. To decrease the amounts of matrix metalloproteinases released into the media during aggrecanase accumulation, agents which inhibit MMP-1, -2, -3, and -9 biosynthesis are included during stimulation. This BNC conditioned media containing aggrecanase activity is then used as the source of aggrecanase for the assay. Aggrecanase enzymatic activity is detected by monitoring production of aggrecan fragments produced exclusively by cleavage at the Glu373-Ala374 bond within the aggrecan core protein by Western analysis using the monoclonal antibody, BC-3 (Hughes, et al., *Biochem J*, [[306]] 305(3):799-804 (1995)). This antibody reportedly recognizes aggrecan fragments with the N-terminus, 374ARGSVIL, generated upon cleavage by aggrecanase. The BC-3 antibody reportedly recognizes this neoepitope only when it is at the N-terminus and not when it is present internally within aggrecan fragments or within the aggrecan protein core. Only products produced upon cleavage by aggrecanase reportedly are detected. Kinetic studies using this assay reportedly yield a K_m of $1.5 \pm 0.35 \mu\text{M}$ for aggrecanase. To evaluate inhibition of aggrecanase, compounds are prepared as 10 mM stocks in DMSO, water, or other solvents and diluted to appropriate concentrations in water. Drug (50 μL) is added to 50 μL of aggrecanase-containing media and 50 μL of 2 mg/ml aggrecan substrate and brought to a final volume of 200 μL in 0.2 M Tris, pH 7.6, containing 0.4 M NaCl and 40 mM CaCl_2 . The assay is run for 4 hr at 37°C, quenched with 20 mM EDTA, and analyzed for aggrecanase-generated products. A sample containing enzyme and substrate without drug is included as a positive control and enzyme incubated in the absence of substrate serves as a measure of background. Removal of the glycosaminoglycan side chains from aggrecan reportedly is

necessary for the BC-3 antibody to recognize the ARGSVIL epitope on the core protein. Therefore, for analysis of aggrecan fragments generated by cleavage at the Glu373-Ala374 site, proteoglycans and proteoglycan fragments are enzymatically deglycosylated with chondroitinase ABC (0.1 units/10 μ g GAG) for 2 hr at 37°C and then with keratanase (0.1 units/10 μ g GAG) and keratanase II (0.002 units/10 μ g GAG) for 2 hr at 37°C in buffer containing 50 mM sodium acetate, 0.1 M Tris/HCl, pH 6.5. After digestion, aggrecan in the samples is precipitated with 5 volumes of acetone and resuspended in 30 μ L of Tris glycine SDS sample buffer (Novex) containing 2.5% beta mercaptoethanol. Samples are loaded and then separated by SDS-PAGE under reducing conditions with 4-12% gradient gels, transferred to nitrocellulose and immunolocalized with 1:500 dilution of antibody BC3. Subsequently, membranes are incubated with a 1:5000 dilution of goat anti-mouse IgG alkaline phosphatase second antibody and aggrecan catabolites visualized by incubation with appropriate substrate for 10-30 minutes to achieve optimal color development. Blots are quantitated by scanning densitometry and inhibition of aggrecanase determined by comparing the amount of product produced in the presence versus absence of compound.

Preliminary Amendment A
Appl. No. 10/618,288
December 12, 2003

CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8

I certify that this correspondence is being deposited with the U.S. Postal Service on **December 12, 2003** with sufficient postage as first class mail (including Express Mail per MPEP §512), and addressed to **Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450**.

A handwritten signature in black ink, appearing to read "David N. T.", is written over a horizontal line.

DMG/PML